Palladium-Catalyzed Direct C-3 Alkynylation of Indolizines with (2,2-Dibromovinyl)arenes

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General

Infrared spectra were recorded with a FTIR spectrometer. NMR spectra were recorded for ^1H NMR at 400 MHz or 500 MHz, and ^{13}C NMR at 100 MHz or 125 MHz using TMS as internal standard. The following abbreviations were used to describe peak patterns where appropriate: singlet (s), doublet (d), doublet of doublets (dd), triplet (t), quartet (q), multiplet (m), broad resonances (br). Mass spectroscopy data of the products were collected on an HRMS-EI-TOF instrument or a low-resolution MS instrument using EI or ESI ionization.

Preparation and Characterization of Starting Materials: ^[1]

Step 1: To a solution of pyridines (100 mmol) in EtOAc (60 mL) was added the appropriate bromoacetic acid (100 mmol). After the mixture was stirred for 3 h at r.t., the solid was filtered and dried in air to give N-(carboxymethyl)pyridinium bromides as white solid.

Step 2: A suspension of N-(carboxymethyl)pyridinium bromides (10 mmol), alkene (50 mmol), Et_3N (1.5 mL) and MnO_2 (80 mmol) in toluene (80 mL) was stirred at 90 °C for 2 h (monitored by TLC). After the mixture was cooled to r.t., the solid was filtered off and washed with acetone. The combined filtrates were evaporated to give a residue, which was purified by chromatography (silica gel, ethyl acetate/petrol ether =1/5) to give the corresponding indolizines stored in the refrigerator.

Typical procedure for the product:

A mixture of indolizines (0.3 mmol), vinyl dibromides (0.9 mmol), Pd(OAc)₂ (7 mg, 10 mol%), DPEPhos (30 mg, 20 mol%), AgOAc (100 mg, 0.6 mmol), CsOAc (170 mg, 0.9 mmol) in DMF (2 mL) was stirred at 100 °C under N₂ for 24 h. Afterward, the mixture was cooled to room temperature, filtered through a pad of celite. The crude product was dissolved in Et₂O (20 mL), washed with water (2 × 20 mL), brine (20 mL), then dried over Na₂SO₄. The solvent was evaporated under reduced pressure, and the residue was subjected to flash column chromatography to obtain the desired product.

Characterization data of the products

3-(Phenylethynyl)indolizine-1-carbonitrile (**3a**) ^[2]

White solid; m.p. 276–278 °C; ¹H NMR (400 MHz, CDCl₃, TMS) δ 8.37 (d, *J* = 6.8 Hz, 1 H), 7.67 (d, *J* = 8.8 Hz, 1 H), 7.56-7.58 (m, 2 H), 7.38-7.39 (m, 3 H), 7.28 (s, 1 H), 7.19 (t, *J* = 7.6 Hz, 1 H), 6.92 (t, *J* = 6.4 Hz, 1 H); ¹³C NMR (100 MHz, CDCl₃) δ 138.0, 131.4, 128.9, 128.5, 125.7, 124.0, 122.1, 121.4, 117.9, 113.8, 97.2, 82.3. HRMS (EI) Calcd for C₁₇H₁₀N₂ (M⁺) 242.0844; Found, 242.0851.

Methyl 3-(phenylethynyl)indolizine-1-carboxylate (3b) ^[2]

White solid; m.p. 254–256 °C. ¹H NMR (400 MHz, CDCl₃, TMS) δ 8.36 (d, *J* = 6.8 Hz, 1 H), 8.23 (d, *J* = 9.2 Hz, 1 H), 7.56-7.58 (m, 2 H), 7.52 (s, 1 H), 7.37-7.39 (m, 3 H), 7.17 (t, *J* = 8.0 Hz, 1 H), 6.88 (t, *J* = 6.8 Hz, 1 H), 3.91 (s, 3 H); ¹³C NMR (100 MHz, CDCl₃) δ 164.7, 136.3, 131.2, 128.5, 125.4, 123.8, 122.7, 121.1, 119.8, 117.9, 113.3, 108.2, 104.0, 97.0, 78.9, 51.1. HRMS (EI) Calcd for C₁₈H₁₃NO₂ (M⁺) 275.0946; Found, 275.0941.

Ethyl 3-(phenylethynyl)indolizine-1-carboxylate (3c) ^[2]

White solid; m.p. 247–248 °C; ¹H NMR (400 MHz, CDCl₃, TMS) δ 8.37 (d, *J* = 6.8 Hz, 1 H), 8.24 (d, *J* = 8.8 Hz, 1 H), 7.56-7.58 (m, 2 H), 7.55 (s, 1 H), 7.36-7.39 (m, 3 H), 7.17 (t, *J* = 8.0 Hz, 1 H), 6.88 (t, *J* = 7.2 Hz, 1 H), 4.36-4.41 (m, 2 H), 1.42 (t, *J* = 7.2 Hz, 3 H); ¹³C NMR (100 MHz, CDCl₃) δ 164.3, 136.2, 131.2, 128.5, 128.4, 125.3, 123.8, 122.7, 121.2, 119.8, 113.3, 108.1, 104.4, 97.0, 79.0, 59.7, 14.6. HRMS (EI) Calcd for C₁₉H₁₅NO₂ (M⁺) 289.1103, Found 289.1106.

n-Butyl 3-(phenylethynyl)indolizine-1-carboxylate (3d) ^[2]

Brown solid; m.p. 260–262 °C; ¹H NMR (400 MHz, CDCl₃, TMS) δ 8.36 (d, *J* = 6.8 Hz, 1 H), 8.23 (d, *J* = 9.6 Hz, 1 H), 7.55–7.58 (m, 2 H), 7.54 (s, 1 H), 7.36–7.38 (m, 3 H), 7.14–7.18 (m, 1 H), 6.87 (t, *J* = 7.6 Hz, 1 H), 4.33 (t, *J* = 6.4 Hz, 2 H), 1.74–1.79 (m, 2 H), 1.48–1.54 (m, 2 H), 1.00 (t, *J* = 7.6 Hz, 3 H); ¹³C NMR (100 MHz, CDCl₃) δ 164.4, 136.2, 131.2, 128.5, 128.4, 125.3, 123.7, 122.7, 121.2, 119.8, 113.2, 108.1, 104.4, 97.0, 78.9, 63.6, 31.0, 19.4, 13.8. HRMS (EI) Calcd for C₂₁H₁₉NO₂ (M⁺) 317.1416; Found, 317.1422.

2-Methyl-3-(phenylethynyl)indolizine-1-carbonitrile (**3e**) ^[2]

White solid; m.p. 293–294 °C; ¹H NMR (400 MHz, CDCl₃, TMS) δ 8.27 (d, *J* = 7.2 Hz, 1 H), 7.54-7.58 (m, 3 H), 7.39-7.40 (m, 3 H), 7.13 (t, *J* = 7.6 Hz, 1 H), 6.86 (t, *J* = 7.6 Hz, 1 H), 2.52 (s, 3 H); ¹³C NMR (100 MHz, CDCl₃) δ 137.4, 133.5, 131.2, 128.7, 128.5, 125.5, 123.8, 122.4, 117.1, 116.0, 113.3, 107.7, 99.6, 83.4, 77.3, 11.4. HRMS (EI) Calcd for C₁₈H₁₂N₂ (M⁺) 256.1000; Found, 256.1001.

3-(o-tolyethynyl)indolizine-1-carbonitrile (4a)

Brown solid; mp 158.9-160.2°C; ^1H NMR (400 MHz, CDCl_3 , TMS) δ 8.38 (d, $J = 8$ Hz, 1 H), 7.70 (d, $J = 8$ Hz, 1 H), 7.54 (d, $J = 8$ Hz, 1 H), 7.28-7.30 (m, 3 H), 7.20-7.22 (m, 2 H), 6.95 (t, $J = 6.4$ Hz, 1 H), 2.56(s, 3 H); ^{13}C NMR (100 MHz, CDCl_3) δ 138.7, 137.0, 130.8, 128.7, 128.0, 124.8, 124.6, 122.8, 121.0, 120.1, 116.9, 115.1, 112.8, 95.2, 81.5, 80.5, 20.0; IR (neat) ν 3105, 2215, 1596, 1504, 1458, 785, 747 cm^{-1} ; HRMS (EI) Calcd for $\text{C}_{18}\text{H}_{12}\text{N}_2$ (M^+) 256.1000; Found, 256.1002.

3-(m-tolylethynyl)indolizine-1-carbonitrile (4b)

Brown solid; mp 160.5-161.5°C; ^1H NMR (400 MHz, CDCl_3 , TMS) δ 8.34 (d, J = 6.8 Hz, 1 H), 7.64 (d, J = 8.8 Hz, 1 H), 7.33-7.36 (m, 2 H), 7.22-7.24 (m, 2 H), 7.13-7.17 (m, 2 H), 6.89 (t, J = 6.4 Hz, 1 H), 2.31(s, 3 H); ^{13}C NMR (100 MHz, CDCl_3) δ 138.3, 131.9, 129.8, 128.5, 125.8, 123.9, 122.5, 122.0, 121.3, 117.9, 113.8, 97.6, 82.4, 21.3; IR (neat) ν 3100, 2215, 1602, 1508, 1463, 785, 747 cm^{-1} ; HRMS (EI) Calcd for $\text{C}_{18}\text{H}_{12}\text{N}_2$ (M^+) 256.1000; Found, 256.1002.

3-((3-fluorophenyl)ethynyl)indolizine-1-carbonitrile (4c)

Brown solid; mp 161.2-162.6°C; ^1H NMR (400 MHz, CDCl_3 , TMS) δ 8.37 (d, $J = 8$ Hz, 1 H), 7.71 (d, $J = 8$ Hz, 1 H), 7.35-7.38 (m, 2 H), 7.31 (s, 1 H), 7.20-7.28 (m, 2 H), 7.07-7.12 (t, $J = 8$ Hz, 1 H), 6.96 (t, $J = 8$ Hz, 1 H); ^{13}C NMR (100 MHz, CDCl_3) δ 162.4(d, $J = 245.3$ Hz), 138.1, 130.2(d, $J = 9.5$ Hz), 127.2(d, $J = 3.4$ Hz), 125.7, 124.2, 121.9, 118.1(d, $J = 22.1$ Hz), 118.0, 116.2(d, $J = 22$ Hz), 115.9, 114.0, 108.4, 96.2, 82.7, 78.7; IR (neat) ν 3104, 2214, 1608, 1579, 1508, 1246 cm^{-1} ; HRMS (EI) Calcd for $\text{C}_{17}\text{H}_9\text{FN}_2$ (M^+) 260.0750; Found, 260.0750.

Brown solid; mp 160.3-161.4°C; ^1H NMR (400 MHz, CDCl_3 , TMS) δ 8.36 (d, J = 8 Hz, 1 H), 7.68 (d, J = 8 Hz, 1 H), 7.34-7.36 (m, 2 H), 7.30 (s, 1 H), 7.22-7.26 (m, 2 H), 7.10 (m, 1 H), 6.96 (t, J = 8 Hz, 1 H); ^{13}C NMR (100 MHz, CDCl_3) δ 162.1(d, J =243.5 Hz), 138.0, 129.8(d, J = 10.1 Hz), 127.20(d, J = 3.6 Hz), 125.4, 124.1, 121.6, 117.9(d, J =22.4 Hz), 118.0, 116.4(d, J =22.6 Hz), 115.7, 113.8, 108.4, 96.2, 82.5, 78.6; IR (neat) ν 3102, 2231, 1612, 1574, 1502, 1238 cm^{-1} ; HRMS (EI) Calcd for $\text{C}_{17}\text{H}_9\text{FN}_2$ (M^+) 260.0750; Found, 260.0750.

3-((4-chlorophenyl)ethynyl)indolizine-1-carbonitrile (**4e**) ^[2]

Yellow solid; m.p. 317–318 °C; ¹H NMR (400 MHz, CDCl₃, TMS) δ 8.36 (d, *J* = 7.2 Hz, 1 H), 7.69(d, *J* = 8.8 Hz, 1 H), 7.49 (d, *J* = 8.0 Hz, 2 H), 7.36 (d, *J* = 8.4 Hz, 2 H), 7.28 (s, 1 H), 7.21 (t, *J* = 8.0 Hz, 1 H), 6.95 (t, *J* = 6.8 Hz, 1 H); ¹³C NMR (100 MHz, CDCl₃) δ 138.0, 134.9, 132.5, 128.9, 125.7, 124.1, 121.7, 120.6, 117.9, 115.9, 113.9, 108.5, 96.2, 82.5, 78.7. HRMS (EI) Calcd for C₁₆H₁₂N₂ (M⁺) 276.0454, Found 276.0457.

3-((4-methoxyphenyl)ethynyl)indolizine-1-carbonitrile (4f) ^[2]

White solid; m.p. 296–297 °C; ¹H NMR (400 MHz, CDCl₃, TMS) δ 8.37 (d, *J* = 8 Hz, 1 H), 7.68 (d, *J* = 8 Hz, 1 H), 7.50-7.53 (m, 2 H), 7.27 (s, 1 H), 7.19 (t, *J* = 8 Hz, 1 H), 6.90-6.93 (m, 3 H), 3.86 (s, 3 H); ¹³C NMR (100 MHz, CDCl₃) δ 160.2, 137.9, 133.1, 125.7, 123.7, 121.0, 117.9, 114.2, 114.1, 113.6, 109.2, 97.2, 82.3, 55.4. HRMS (EI) Calcd for C₁₈H₁₂N₂O(M⁺) 272.0950; Found, 272.0950.

3-((4-(tert-butyl)phenyl)ethynyl)indolizine-1-carbonitrile (4g)

Brown solid; mp 164.0-165.1°C; ^1H NMR (400 MHz, CDCl_3 , TMS) δ 8.37 (d, $J = 8$ Hz, 1 H), 7.68 (d, $J = 8$ Hz, 1 H), 7.50-7.52 (m, 2 H), 7.40-7.43 (m, 2 H), 7.27 (s, 1 H), 7.19 (t, $J = 8$ Hz, 1 H), 6.93 (t, $J = 8$ Hz, 1 H); ^{13}C NMR (100 MHz, CDCl_3) δ 152.4, 137.9, 131.2, 125.8, 125.6, 123.9, 121.2, 119.1, 117.9, 116.2, 113.7, 109.1, 97.5, 82.3, 34.9, 31.2; IR (neat) ν 3098, 2923, 2216, 1511, 1463, 835, 747 cm^{-1} ; HRMS (EI) Calcd for $\text{C}_{21}\text{H}_{18}\text{N}_2(\text{M}^+)$ 298.1470; Found, 298.1465.

3-((3-nitrophenyl)ethynyl)indolizine-1-carbonitrile (4h)

Brown solid; mp 175.4-176.3°C; ^1H NMR (400 MHz, CDCl_3 , TMS) δ 8.40 (m, 2 H), 8.23 (d, J = 8 Hz, 1 H), 7.86 (d, J = 8 Hz, 1 H), 7.73 (d, 1 H), 7.60 (t, J = 8 Hz, 1 H), 7.37 (s, 1 H), 7.25 (m, 1 H), 7.01 (t, J = 8 Hz, 1 H); ^{13}C NMR (100 MHz, CDCl_3) δ 138.4, 136.7, 129.7, 126.0, 125.8, 124.5, 124.1, 123.9, 123.3, 122.6, 118.1, 115.7, 114.3, 107.8, 95.1, 83.1, 80.5; IR (neat) ν 3100, 2214, 1602, 1521, 1463, 1345, 903, 745 cm^{-1} ; HRMS (EI) Calcd for $\text{C}_{17}\text{H}_9\text{N}_3\text{O}_2(\text{M}^+)$ 287.0695; Found, 287.0697.

3-(4-Cyano-phenylethynyl)-indolizine-1-carbonitrile (4i)

Yellow solid; mp 173.9-175.1°C; ^1H NMR (400 MHz, CDCl_3 , TMS) δ 8.37 (d, $J = 8$ Hz, 1 H), 7.71 (d, 1 H), 7.62-7.68 (m, 4 H), 7.35 (s, 1 H), 7.23 (s, 1 H), 6.99 (t, 1 H); ^{13}C NMR (100 MHz, CDCl_3) δ 175.1, 138.4, 132.3, 131.5, 127.1, 125.7, 124.6, 122.7, 118.8, 118.3, 118.1, 115.7, 114.3, 111.9, 107.9, 96.1, 83.2, 82.3; IR (neat) ν 3100, 2921, 2221, 2198, 1540, 1509, 1487, 1463, 835, 747 cm^{-1} ; HRMS (EI) Calcd for $\text{C}_{18}\text{H}_9\text{N}_3(\text{M}^+)$ 267.0796; Found, 267.0794.

3-((3-methylthiophen-2-yl)ethynyl)indolizine-1-carbonitrile (4j)

Yellow solid; mp 164.8-166.1°C; ^1H NMR (400 MHz, CDCl_3 , TMS) δ 8.35 (d, $J = 8$ Hz, 1 H), 7.70 (d, $J = 8$ Hz, 1 H), 7.29 (s, 1 H), 7.25-7.27 (m, 2 H), 7.21 (m, 1 H), 6.93 (m, 1 H), 2.41 (s, 3 H); ^{13}C NMR (100 MHz, CDCl_3) δ 143.7, 138.1, 129.5, 127.2, 125.8, 124.0, 121.7, 118.0, 117.5, 116.1, 113.9, 108.9, 90.0, 83.2, 82.6, 15.3; IR (neat) ν 3106, 2921, 2217, 1513, 1463, 747 cm^{-1} ; HRMS (EI) Calcd for $\text{C}_{16}\text{H}_{10}\text{N}_2\text{S}(\text{M}^+)$ 262.0565; Found, 262.0568.

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